UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,303	11/04/2005	Peter Bernstein	133087.12001(100819-1PUS)	5966

52286 7590 08/10/2007

Pepper Hamilton LLP
500 Grant Street
One Mellon Bank Center, 50th Floor
Pittsburgh, PA 15219-2502

EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,303	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10 and 12-17* is/are rejected.

7)☒ Claim(s) *4 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8, 10, 12-17 are pending in the current application.

2. The instant application is a 371 of PCT/SE2003/001329, filed August 26, 2003, which claims the priority of Application No. 0202567-4 filed in Sweden on August 29, 2002 and Application No. 0202986-6 filed in Sweden on October 9, 2002.

Response to Arguments

3. Applicant's arguments filed on July 3, 2007 have been fully considered but they are not persuasive. The rejections of claims 9 & 11 are withdrawn since they have in fact been canceled. With respect to the objection, the specification has been duly amended and the examiner appreciates this correction and withdraws the objection. Since "in-vivo hydrolysable precursor" has been removed from the claims, the written description rejection is withdrawn. With respect to the rejection under 35 U.S.C. 112 1st paragraph for **scope** of enablement in regards to the compound claims, applicant's detailed arguments will be dealt with in turn as the rejection is restated, applied to new claims and maintained for the reasons of record (*vide infra*) [claims 1-3, 5-7, new claims 12-14]. The rejections under 35 U.S.C. 112 1st paragraph for **lack** of enablement for treating various diseases and disorders with the compounds of the instant case is also maintained for the reasons of record [8, 10, new claims 16, 17]. With respect to claims 8, 10 (and now 16 and 17) the applicant has argued (remarks at 34):

"It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning....."

which the examiner agrees with completely and is why the scientific basis of the rejection is succinctly explained replete with two scientific publications detailing the state of the art in NK-1

antagonists/SRI, which is why the statement on remarks (pg. 35) is completely incongruous with the record:

"The Office has failed to set forth any reasoning or evidence to support the rejection or provided any objective evidence of non-enablement. (emphasis added). Accordingly, the Office has not established a prima facie case of non-enablement. Failing to do so, the burden has not properly shifted to Applicants."

It is noted that no rebuttal of the scientific rational for the enablement rejection has been made and appears to have been ignored. The two cited publications are McLean, S. *Current Pharmaceutical Design* **2005**, *11*, 1529. & Rosenzwieg-Lipson et. al. *Pharmacology & Therapeutics* **2007**, *113*, 134-153, which contain not the subjective statements of the office but objective statements from those in the field testifying to the state of the art. To reiterate the position and further clarify, the only information provided to us for evaluation of treatment of diseases ranging from "kleptomania" to "Alzheimer's" are some very preliminary cell based assays on receptors/transporters that are not clearly linked to any of these disease states.

Claim Rejections 35 U.S.C 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 5-7, 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds of structural diagram I (claim 1), it does not reasonably provide enablement for the multivariate structures contained in the claim where R^1-R^2 are varied substituents. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to prepare the compounds of the invention commensurate in scope with these claims. As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. **The same can be said if certain chemicals are required to make a compound or practice a chemical process**. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). (emphasis added)

Based on applicants disclosure (on pages 16 and 17 of the specification, reproduced below for clarity),

The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

a) 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine.

- 17 -

To a stirred solution containing 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine (260.8 mg, 0.726 mmol), 3-cyano-2-methoxy-1-naphthoic acid (164.6 mg, 0.724 mmol), HOBT hydrate (290 mg, 1.89 mmol), N-methylmorpholine (0.17 mL), and DCM (15 mL) was added 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (215.5 mg, 1.12 mmol). After 72h, the mixture was diluted with 30% hexane/EtOAc, washed successively with water (2X), 0.1 N aq. HCl (2X), sat. aq. $NaHCO_3$, dried, filtered, and concentrated. The residue was purified by chromatography (0-1% MeOH/DCM) to give the title compound as a white, foamy solid. MS m/z 468.

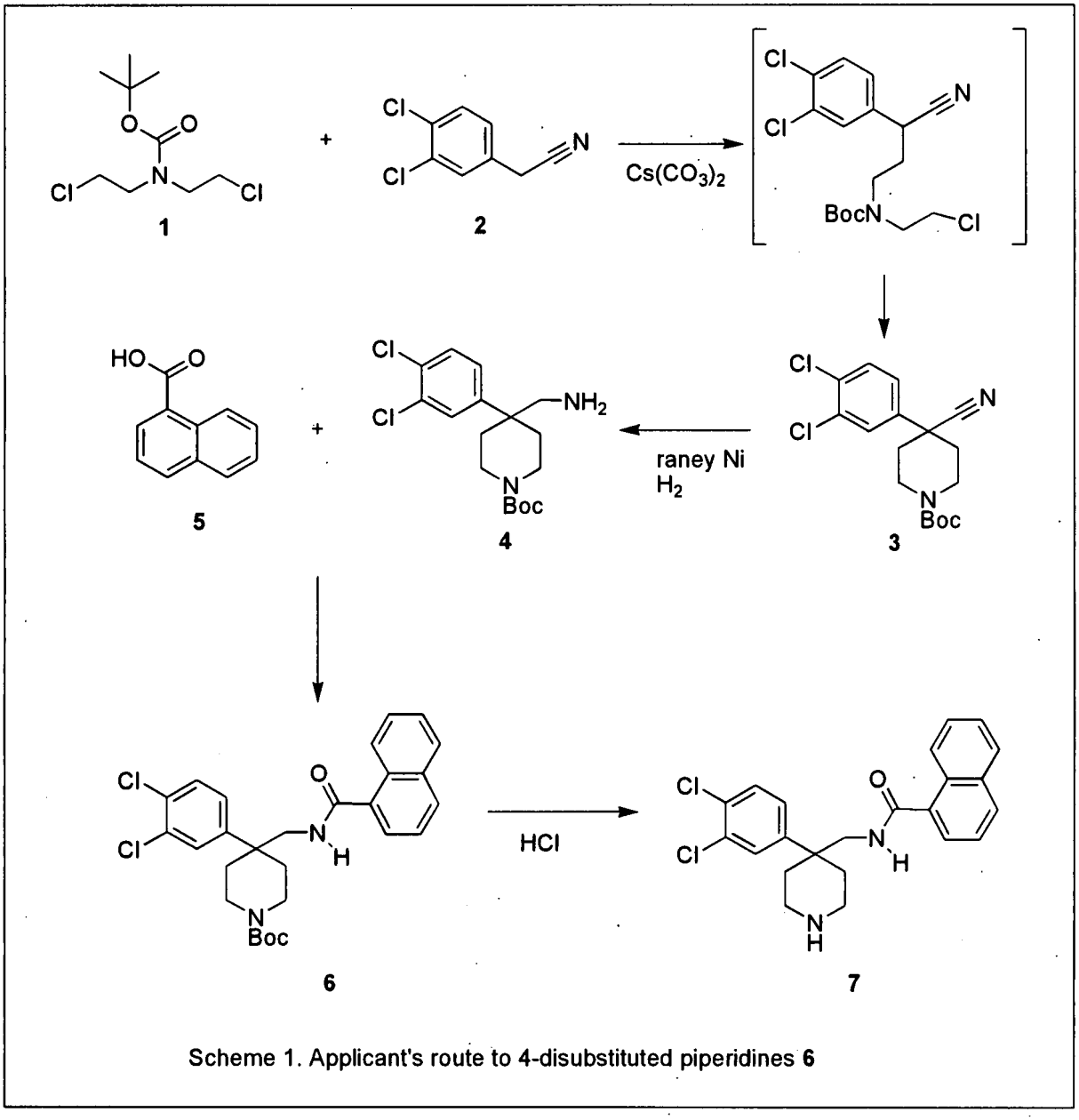
b) 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine

A mixture containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine (5.25 g, 14.78 mmol), Raney Ni catalyst (5g of 50% aq. slurry), EtOH (175 mL), and ammonium hydroxide (88 mL) was placed under a hydrogen atmosphere (50 psi) and agitated (Parr apparatus) for 18 h. The mixture was filtered through diatomaceous earth, concentrated, and purified by chromatography (0-5% MeOH/DCM) to give the title compound as an off-white solid. MS m/z 344 ($M+1-CH_3$). 1H NMR ($CDCl_3$) δ 7.44 (d, 1H), 7.38 (d, 1H), 7.15 (m, 1H), 3.7 (br d, 2H), 3.07 (m, 2H), 2.76 (s, 2H), 2.08 (br d, 2H), 1.71 (m, 2H), 1.44 (s, 9H).

c) 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine

A solution containing bis(2-chloroethyl)-N-BOC amine (described in US Patent 5,661,163) (8.15 g, 33.67 mmol), 3,4-dichlorophenylacetonitrile (5.05 g, 27.17 mmol), and DMSO (50 mL) was stirred at RT and solid cesium carbonate (17.6 g, 54.02 mmol) was added (in portions) over 10 minutes. After 20 h, additional cesium carbonate (1.7 g,) was added, and the mixture stirred for an additional 72 h. The mixture was partitioned between water and EtOAc, the aq. layer was removed, and the organic layer washed successively with additional water, 0.1M aq. HCl (2X), sat. aq. $NaHCO_3$, and brine. The organic layer was dried, filtered, concentrated, and the residue triturated (3:1 hexane/ethyl acetate) to give the title compound as an off-white solid, m.p. 142-145 °C. MS m/z 255 . 1H NMR ($CDCl_3$) δ 7.55 (d, 1H), 7.49 (d, 1H), 7.32 (m, 1H), 4.3 (br d, 2H), 3.18 (br t, 2H), 2.07 (d, 2H), 1.89 (m, 2H), 1.48 (s, 9H).

Scheme 1 was constructed and is presented here for discussion of the synthetic route to these compounds and the limitations therein.



Scheme 1. Applicant's route to 4-disubstituted piperidines **6**

Compounds bearing a vast list of possibilities for R1, R^2, R^3, R^4 have been claimed in claims 1-3 and very little guidance has been provided on how to do so. A detailed discussion of each limitation of the synthesis as it relates to the claims at hand

(claims 1-3) will be provided. The applicant needs substituted benzyl nitriles of the type **2** (Scheme 1) and no guidance has been given as to how one might arrive at these compounds. These are very specialized compounds and *we are not given a route to a single one*? Most of them are not commercial compounds. We are not told how to make them, thus the public cannot be in possession of the invention if they cannot make it. Applicant has stated that Ong et. al. *J. Med. Chem.* **1983**, *26*, 981-986 (cited by the examiner) shows how to make these compounds, which is incorrect since Ong et. al. has only used two of these compounds one unsusbstituted and the other substituted with Cl and has not actually made any but rather employed them as starting materials. The main thrust of applicant's argument appears to be that a chemist can simply make any compound at will, which is inconsistent with the state of the art. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially

> chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

If the vast array of compounds **2** were available many will not participate in the synthesis given (Scheme 1), thus the scope of the claimed substituents R_4 is not enabled. In particular where **2** and thus R_4 is a nucleophile such as "NR^aR^b, $CH_2NR^aR^b$, SR^a, CH_2OR^a, OR^a, $C(O)R^c$," will attack the dichloride **1**, preferentially leading to other products. The applicant has argued that Ra may be other than H, which is true, however it is also H nonetheless. The use of Raney Ni/H_2 necessarily precludes many substituents listed as R_4, in claims 1-3. The following groups for R_4 are not enabled due to the use of Raney Ni/H_2:

A) "$(CH_2)jG(CH_2)k$ or $G(CH_2)jG$, where G is oxygen or sulfur, j is l, 2, 3 or 4, and k is 0, 1 or 2; m is l, 2 or 3 where at least one R moiety is other than hydrogen...."; "R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, and n is 0, 1, 2 or 3..." and "SR^a". Groups that contain sulfur will undergo desulfurization, as is well known in the art (Hauptman and Walter, *Chem. Rev.* **1962**, *62*, 347.)

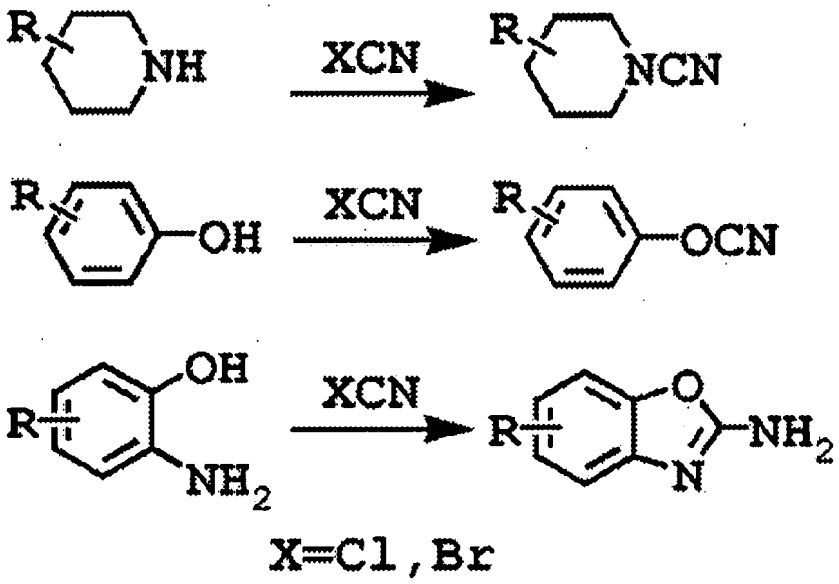
B) Surprisingly nitrile (CN) is listed as a possible permutation of Formula I's R_4, yet we know from the disclosure that this nitrile will be reduced to the amine with Raney Ni/H_2 (**3** to **4**, Scheme 1). Thus it is not enabled.

C) Olefins and alkynes, where R_4 is C_{2-4}alkenyl, C_2-C_4alkynyl, will be reduced as is well known in the art (Fieser and Fieser, *Reagents for Organic Synthesis*, Vol. 1 Wiley: NY, 1974, pg. 723-730).

D) Ketones and aldehydes where R_4 is $C(O)R_c$, or CO_2R_c can also be reduced as is known is the art (Mitchell and Lai *Tetrahedron Letters* **1980**, *21*, 2637).

E) Where R_4 halogen and in the ortho (2-position relative to the benzyl nitrile) of the phenyl ring, upon reduction of the nitrile an intramolecular cyclization will occur to give spirocyclic indolo-piperidines as taught by Ong et. al. *J. Med. Chem.* **1983**, *26*, 981-986. It is also known that Raney/Ni will dehalogenate aryl halides, resulting in what is formally a replacement of halogen with hydrogen (Fieser and Fieser, *Reagents for Organic Synthesis*, Vol. 1 Wiley: NY, 1974, pg. 726), although applicant seems to have provided conditions that prevent this reaction.

The applicant has argued that $LiAlH_4$ would overcome the deficiencies of Raney/Ni in terms of selectivity and the examiner agrees at least in terms of the intramolecular cyclization however this reagent too has its own set of limitations and is a very promiscuous reductant that will react with nearly any electrophilic functional group ("Lithium Aluminum Hydride" Paquette, L. in *Encyclopedia of Reagents for Organic Synthesis* Online Posting Date: October 15, 2004 John Wiley & Sons, Ltd. "http://www.mrw.interscience.wiley.com/eros/articles/rl036/frame.html") Nitriles are known to be reduced by $LiAlH_4$ (Amundsen, L.H. et. al. *J. Am. Chem. Soc.* **1951**, *73*, 242-244). The applicant's have then suggested that the final product could undergo direct cyanation. With cyanogen bromide or some other electrophilic CN source? The piperidine will be cyanated, as well as phenolic OH's etc.



Regardless these reactions depend upon an electron rich arene and in the instant case there seems to be a real requirement for Ar to bear electron withdrawing groups.

F) Applicant also makes claims to compounds where R_2 is other than H (claims 1-4 and dependent) and no guidance is provided as to how we can arrive at these compounds. It would seem that a starting material as shown in Figure 1, is required, yet we do not have any guidance as to how one may obtain such compounds.

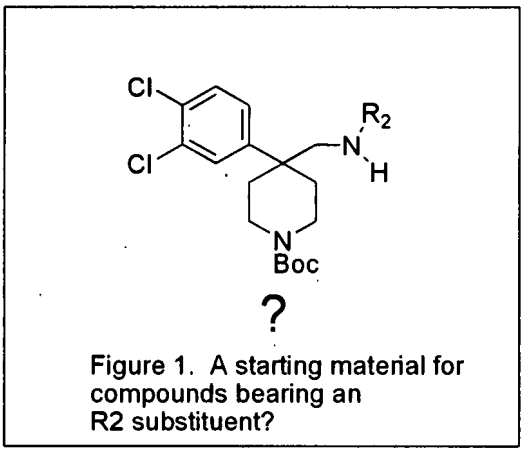


Figure 1. A starting material for compounds bearing an R2 substituent?

G) In addition the naphthoic acids such as **5** (Scheme 1) required for the scope of this invention are not commercial. Thus the substituent R_1 depends upon these compounds It is recognized that applicant makes reference to a prior commonly assigned application WO 00/20389 for the preparation of a good portion of these and these will be considered allowable, particularly where applicant has working examples in synthetic schemes, but no others.

Another serious consideration is the "how to use" requirement of 112 1st which mandates that this genus must be constructed such that the members have the property of NK1/SRI activity. What are the effects of theses long alkyl chains or 10 sulfur atoms? We do not know but in this case the members of the genus bear no structural resemblance to one another and even if they did the situation is far from clear that they would have the desired activity. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions)

As per MPEP:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and

whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)

As applied to the claims at hand (claims 1-3, 5-7, 12-14):

A) The claims are very broad. B) This is a chemical invention, thus we need to be able to make the compounds in order to use them. C) The state of the art shows that many reactions can occur with compounds **2** D) The level of ordinary skill is one with a basic knowledge of organic chemistry E) Chemistry is inherently unpredictable (*In re Marzocchi*, 169 USPQ 367, *In re Fischer*, 166 USPQ 18). F) The inventor gives us little or no guidance (especially on the origin of compound **2.**) G) The applicant has no working examples of the substituents listed above. H) An undue amount of experimentation would be needed to make these compounds.

6. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 12 of the disclosure "Individual IC_{50} values were reported, along with pIC_{50}. When the two IC_{50}'s obtained for a compound differed by more than 3-fold that compound was assayed one or two more times to redetermine the value. Compounds of the present invention exhibit a

Ki in the range of 1 to 100 nM in the SERT assay and have an IC_{50}'s in the range 1 to 100 nM in FLIPR assay." The applicant has given ranges of two orders of magnitude for each individual assay, without reference to a known compound that is an agonist/inhibitor and the variability in these assays make evaluation of therapeutic value difficult. For example in the case of the NK-1 receptor in transfected cells, overexpression of a GPCR can lead to many false positives in a FLIPR assay, due to high constitutive activity and the low threshold of activation. The situation is further compounded by the fact that it is possible for a single compound to be very different things at each target. In the instant case we do not know whether the compounds are partial agonists at the NK-1 receptor. It is possibly that some compounds are both SERT inhibitors and partially active at the NK-1 receptor and vice versa, or both potent inhibitors of SERT and potent antagonists at the NK-1 receptor. Applicant seems to believe these compounds are the later although no support has been provided for this assertion. Moreover, even if this dual activity was possessed by the compounds of the invention, one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of claim 10. The article cited by the authors (Ryckmans, T., et al., Bioorg. Med. Chem.Lett. (2002), 12, 261). suggests that these kinds of compounds might be useful for treatement of depression and they may well be but no such evidence is provided in the instant case. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). In regard to claim 10, depression is the only disease where such treatment *might* be efficacious, however this is not indicated, even with pre-

clinical data (animal models), as stated in a recent review (Rosenzwieg-Lipson et. al. *Pharmacology & Therapeutics* **2007**, *113*, 134-153) pg. 140 paragraph 3 sentence 2:

> "**Although the NK-1 antagonist aprepitant was not proven efficacious in Phase III depression trials (Keller et al., 2006), it is conceivable that the combination of aprepitant with an SSRI might result in rapid onset of antidepressant effects. To this end, NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies** (Guiard et al., 2004). **Whether this combination or other non-monoaminergic mechanisms will produce rapid onset antidepressant effects remains to be answered.**"

Thus the state of the art in the area of these dual antagonists is murky at best. Even if there was a correlation of the pharmacological activity with a clinical manifestation, we have only *in-vitro* testing of these compounds and no *in-vivo* data. Without at least animal studies of *in-vivo* activity one cannot believe that these compounds will behave as therapeutics in those suffering from depression. Moreover, even if these compounds were evaluated simply as NK-1 antagonists, a recent review article (McLean, S. *Current Pharmaceutical Design* **2005**, *11*, 1529, pg. 1542 paragraph 3) states, that:

> In summary, clinical studies with three different compounds demonstrate antidepressant efficacy in both mildly depressed as well as melancholic patients. Furthermore, the favorable side effect profile of the agents suggests a viable therapy particularly for people experiencing significant sexual side effects with currently available antidepressants. **This has to be balanced against a number of trials in which NK1 receptor antagonists failed to show activity. In addition to the previously mentioned negative trials, NKP608 another NK1 receptor antagonist was reported on the Novartis web site to have been terminated from further development for depression although it is unclear whether this was due to side effects or lack of efficacy. To date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies.**

It seems very unlikely that one skilled in the art would know what to do with these compounds. The other exhaustive list of diseases in claim 10 are not even remotely related (kleptomania, premature ejaculation, parkinson's, alzheimer's, child abuse etc.) and the data given here have no credibility for treatment given the mechanism that applicant alleges and the current knowledge in the art.

As per MPEP:

CORRELATION: IN VITRO /IN VIVO
The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. **If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.** In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

The factors outlined in *In re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to use"...."the claimed invention without undue experimentation. *In re Wright* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Objections

9. Claim 4 and claim 15 are objected to for depending on a rejected base claim but would be allowable if put in proper dependent form. Although they are remarkable similar to the compounds of the invention of Bao et. al PCT/US99/25066 and U.S. Patent 6,303,637, (Bao claims naphthyl, but fails to make them, the only difference between compounds of the '637 patent and the instant case, however the utility is different). After further consideration, the other feature of the potentially allowable claims is the nitrile group in a very precise position, without this substitution the broad claims if enabled would be obvious over the prior art, based on recent jurisprudence (*KSR v. Teleflex*).

Conclusion

9. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

10. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER

8/6/07